Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Nutrition management guideline for maple syrup urine disease: an evidence- and consensus-based approach.

Bibliographic Source(s)

Frazier DM, Allgeier C, Homer C, Marriage BJ, Ogata B, Rohr F, Splett PL, Stembridge A, Singh RH. Nutrition management guideline for maple syrup urine disease: an evidence- and consensus-based approach. Mol Genet Metab. 2014 Jul;112(3):210-7. [72 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (A-E) and the strength of the recommendation (I, II) are provided at the end of the "Major Recommendations" field.

Acute Dietary Treatment

1. Provide aggressive nutrition management during illness or at first presentation to prevent or reverse catabolism and promote anabolism by supplying: adequate energy (up to 150% of usual energy intake); branched chain amino acids (BCAA)-free protein (increased to replace BCAA-containing intact protein); fluid (up to 150 mL/kg with careful monitoring of electrolytes and possible cerebral edema); and electrolytes and insulin (if needed). (B.I)
2. Use parenteral nutrition alone (providing BCAA-free amino acids, lipids and/or glucose) or in conjunction with enteral feedings, when necessary to meet energy needs in severe illness. (B.II)
3. Include nutritional intervention when dialysis, hemoperfusion or similar treatment is necessary to lower plasma BCAA and remove toxic metabolites. (C.II)
4. Monitor BCAA, acid–base balance, urine α-ketoacids, blood glucose and clinical symptoms closely during illness. If hemofiltration or dialysis is necessary, blood gas, hematocrit, total protein, sodium, calcium, phosphorus, urea, and creatinine should also be monitored. (B.I)
5. Add isoleucine (ILE) and valine (VAL), even if they are already in the 200–400 μmol/L range, to help lower elevated plasma leucine (LEU) into the treatment range. (B.II)
6. Reintroduce intact protein (or complete amino acid mixtures) when elevated plasma LEU approaches the upper limit of the treatment range: 200 μmol/L for infants and children ≤5 years of age; and 300 μmol/L for individuals >5 years of age. (B.I)

7. Consider use of breast milk (mean LEU concentration of 1 mg/mL) as a source of intact protein (and BCAA) in the dietary management of infants with maple syrup urine disease (MSUD) if there is frequent anthropometric, clinical, and laboratory monitoring of the infant and mother has adequate milk production. (D.I)
8. Manage mild illnesses with patient-specific sick-day instructions to include reduction of intact protein by 50% to 100% for 24 to 48 hours by replacement with additional BCAA-free medical food, adequate hydration, addition of non-protein energy sources, and close monitoring. (D.II)

Achieving Appropriate BCAA Blood Concentrations

1. Maintain plasma LEU concentrations, with frequent monitoring, between 75 and 200 µmol/L for infants and children ≤5 years old and between 75 and 300 µmol/L for individuals >5 years of age to achieve favorable cognitive outcomes. (B.I)
2. Maintain plasma ILE and VAL concentrations, with frequent monitoring, between 200 and 400 µmol/L (or slightly above the normal ranges) in all individuals to avoid metabolic instability and BCAA deficiencies. (B.I)
3. Employ MSUD-specific dietary management strategies to achieve recommended BCAA concentrations. (A.I) (see Tables 3 and 4 in the original guideline document).
4. Maintain plasma BCAA within the recommended ranges throughout life. (C.II)

Thiamin Supplementation

1. Perform a thiamin challenge for all individuals with MSUD except those known to be homozygous for the 1312T>A mutation or other mutations resulting in less than 3% branched-chain α-ketoacid dehydrogenase (BCKD) enzyme activity. (B.II)
2. Initiate a thiamin challenge with a dosage of 50–200 mg/day. (C.I)
3. Evaluate response to thiamin challenge over a one month period by assessing plasma BCAA and/or tolerance for dietary BCAA. (D.II)
4. Maintain thiamin supplementation and appropriate dietary BCAA restriction in thiamin-responsive individuals. (D.II)

Pregnancy and Postnatal Period in Women with MSUD

1. Monitor closely and provide individualized dietary guidance to assure that intake is adequate to meet the increased protein, BCAA and energy requirements of pregnancy. (B.I)
2. Maintain plasma BCAA concentrations in the normal (MSUD) treatment range (LEU: 75–300 µmol/L; ILE and VAL: 200–400 µmol/L) throughout pregnancy. (B.I)
3. Treat pregnancy-related poor appetite, nausea and vomiting aggressively to prevent or minimize endogenous protein catabolism. See treatment strategies to prevent endogenous catabolism in Research Question 1 (see the "Description of Methods Used to Collect/Select the Evidence" field). (A.I)
4. Evaluate the need for vitamin and/or mineral supplementation based on the pregnant woman's prescribed medical food, dietary adherence and laboratory assessment. (D.II)
5. Pay special attention to the prevention of catabolism during particularly vulnerable periods of labor/delivery and the first two weeks postpartum, as well as up to six weeks postpartum. (C.I)
6. Provide increased nutrient intake and close clinical and biochemical monitoring for the woman with MSUD who is breastfeeding. (D.I)

Liver Transplantation in Individuals with MSUD

1. Consider liver transplantation as a viable treatment option for individuals with MSUD. (B.II)
2. Attempt to bring candidates for liver transplant into good metabolic control (prior to surgery) through dietary management of BCAA. (C.II)
3. Prevent metabolic decompensation in the perioperative period. (B.I)
4. Allow relaxation of the BCAA-restricted diet and lift precautions for severe metabolic decompensation for individuals with MSUD who have had successful liver transplantation. (C.I)
5. Provide nutrition counseling to assist in dietary transition, and monitor the anthropometric and nutritional status of individuals with MSUD who have had successful liver transplantation. (E.II)

Definitions:

Recommendation Ratings and Application

Recommendation Rating		
A	Strong	The benefits clearly exceed the harms (or the harms clearly exceed the benefits in the case of a strong negative recommendation); and the quality of the supporting evidence is excellent/good. In some clearly identified circumstances,

		strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.
B	Fair	The benefits exceed the harms (or the harms clearly exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong as "A". In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.
C	Weak	The quality of evidence that exists is suspect or well-done studies show little clear advantage for one recommendation over another.
D	Consensus	Expert opinion supports the recommendation even though the available scientific evidence did not present consistent results, or controlled trials were lacking.
E	Insufficient Evidence	There is a lack of pertinent evidence and this may be due to an unclear balance between benefits and harms.
Clinical Action/Application		
I	Imperative	The recommendation is broadly applicable to the target population without conditions. An imperative recommendation can be stated in "require," or "must," or "should achieve certain goals" terminology.
II	Conditional	The recommendation clearly defines a specific situation that limits its applicability. A conditional recommendation can be stated in "if/then" terminology.

Adapted for this guideline from: American Academy of Pediatrics Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. Pediatrics 2004; 114(3):874–7.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Maple syrup urine disease (MSUD)

Guideline Category

Management

Treatment

Clinical Specialty

Emergency Medicine

Family Practice

Internal Medicine

Nephrology

Neurology

Nutrition

Obstetrics and Gynecology

Pediatrics

Urology

Intended Users

Advanced Practice Nurses

Dietitians

Health Care Providers

Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To foster optimum nutrition management of individuals with maple syrup urine disease (MSUD) and reduce the uncertainty and variability in the management of this inherited metabolic disorder (IMD)

Target Population

Individuals with maple syrup urine disease (MSUD) at all life stages from the acute newborn period, through childhood and adolescence, to ongoing management in the adult years and during pregnancy

Interventions and Practices Considered

1. Specialized nutrition management throughout life
2. Aggressive nutrition management during acute illness/sickness
3. Achieving and maintaining appropriate plasma branched chain amino acid (BCAA) concentrations
4. Thiamin supplementation
5. Monitoring pregnancy and postnatal period
6. Liver transplantation

Major Outcomes Considered

- Quality of life
- Adverse outcomes
- Appropriate growth and health maintenance
- Neurocognitive development

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Search Process

Because of the known scarcity of peer-reviewed scientific literature in nutrition management of inherited metabolic disorders (IMDs), the search process included both published scientific studies and gray, or practice, literature.

For the peer-reviewed literature, medical subject heading (MeSH) terms were specific to each question, but inclusion and exclusion criteria were the same for all questions (see questions below). Eligibility for research questions was limited to human studies and published in English from 1985 to summer 2011 (except for the research question related to thiamin that used earlier references from 1971), with nutrition data included. There were no study-design, age or setting restrictions. PubMed was the primary database used. Searches were conducted by a research librarian. The titles and abstracts of identified articles were scanned for relevance and matched with inclusion/exclusion criteria by the workgroup. Excluded articles were noted and qualifying articles were gathered for review and abstracting. Reference lists within the identified articles were examined for additional resources. These were added if they contributed pertinent information.

Practice (or gray) literature sources, which are not accessible through standard search systems, include abstracts and presentations from scientific and practice-based meetings, clinical protocols and guidelines, unpublished research, communication among experts (including list-serves), professional newsletters, and book chapters. The search for gray literature involved requests to individuals (e.g., practitioners and researchers) and organizations through their professional list serves, as well as online searches for materials related to nutrition and maple syrup urine disease (MSUD). Identified resources were screened and prioritized for inclusion based on relevance and substantive information not available in scientific literature, and currency.

Question 1: For the individual with MSUD or suspected MSUD, what nutritional interventions must be initiated during illness, trauma or surgery to achieve optimal outcomes?

- Search Terms: MSUD or maple syrup urine disease, or branched chain alpha keto acid dehydrogenase deficiency, or BCKAD deficiency AND treatment, or management, or symptoms, or dialysis
- Date of Literature Search Request: June 1, 2011

Question 2: For the individual with MSUD treated through dietary modification, what are BCAA blood levels that lead to optimal nutritional, medical and quality of life outcomes?

- Search Terms: MSUD or maple syrup urine disease, or inborn errors of metabolism or branched chain alpha keto acid dehydrogenase deficiency. BCKAD deficiency, AND leucine, or branched chain amino acids, or outcome, or monitoring
- Date of Literature Search Request: June 1, 2011

Question 3: For the individual with MSUD, what is the most effective method for initiating, dosing and evaluating response to thiamin supplementation?

- Search Terms: MSUD or maple syrup urine disease, or inborn errors of metabolism or branched chain alpha keto acid dehydrogenase deficiency. BCKAD deficiency, or aminoacidopathies AND thiamin, or thiamine, or thiamin response, or thiamin responsivity, or thiamin challenge, or thiamin supplementation, or thiamin activation, or thiamine pyrophosphate, or treatment
- Date of Literature Search Request: June 1, 2011

Question 4: For the woman with MSUD, what specific nutritional interventions must be initiated during pregnancy, at delivery and during the postpartum period to achieve optimal outcomes for her and her newborn infant?

- Search Terms: MSUD or maple syrup urine disease, or inborn errors of metabolism or branched chain alpha keto acid dehydrogenase deficiency, or BCKAD deficiency, or maternal MSUD AND pregnancy, or labor and delivery, or pregnancy complications
- Date of Literature Search Request: June 1, 2011

Question 5: For the individual with MSUD undergoing liver transplantation, what specific nutritional interventions result in optimal nutritional, medical and quality of life outcomes?

- Search Terms: MSUD or maple syrup urine disease, or inborn errors of metabolism or branched chain alpha keto acid dehydrogenase deficiency. BCKAD deficiency, AND liver transplant, AND transplant outcome, or long term outcome, or complications, or treatment, or nutrition
- Date of Literature Search Request: June 1, 2011

Number of Source Documents

Number of studies initially identified: 229

Number of studies included: 98

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Not Given)

Rating Scheme for the Strength of the Evidence

Not stated

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Critical Appraisal and Abstraction

Each scientific article was critically reviewed by a trained analyst using a Quality Criteria Checklist, and the study design and methodology, findings, and author's conclusions were abstracted to Evidence Abstract Worksheets. Quality criteria addressed subjects' and control groups' selection and retention, intervention clearly described and followed, other intervening variables tracked, outcomes defined, measures validated, and appropriate statistical analysis. Based on the number of criteria met, each article was assigned a quality rating of positive, neutral or negative.

Practice resources were reviewed by workgroup members using a specially developed quality criteria checklist for gray literature that included the following: clear purpose, relevance to intended users, systematic development process, and clear clinical recommendations, applicable to practice, and free of conflict of interest.

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Expert Consensus (Nominal Group Technique)

Description of Methods Used to Formulate the Recommendations

Question Formulation

The maple syrup urine disease (MSUD) workgroup consisted of eight experienced metabolic dietitians who began the process by independently identifying over 40 practice areas where uncertainty and/or variation in practice existed. These were categorized and prioritized. Five topics were identified for evidence analysis and guideline development. Research questions for each topic were formulated in the PICO (population,

intervention, comparison, and outcomes) format.

Consensus Input and Evidence Summary

Key information from all eligible evidence sources (scientific and gray literature) for each question was summarized on an evidence table. Many issues of concern to nutrition management were not addressed or were inconclusive from the combined sources. For these issues, expert input from nutrition and medical clinicians and researchers was sought using a Delphi survey, nominal group process meeting and a second-round Delphi survey. By systematically employing these techniques, the level of agreement with a specific practice statement was quantified. Also, input from the target population (patient and family) was included in the nominal group process. The final conclusion statement for each question represented a synthesis of evidence from scientific publications, gray literature, and Delphi and nominal group consensus techniques.

Guideline Development

Specific recommendations for nutrition management in each of the five topic areas were derived from the summaries, and each recommendation was rated with respect to strength (A = strong, B = fair, C = weak, D = consensus, E = insufficient evidence) and need for clinical action (I = imperative or II = conditional). See the "Rating Scheme for the Strength of the Recommendations" field.

These practice recommendations along with background and other information to support their implementation are contained in the MSUD Nutrition Management Guideline document.

Rating Scheme for the Strength of the Recommendations

Recommendation Ratings and Application

Recommendation Rating		
A	Strong	The benefits clearly exceed the harms (or the harms clearly exceed the benefits in the case of a strong negative recommendation); and the quality of the supporting evidence is excellent/good. In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.
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C	Weak	The quality of evidence that exists is suspect or well-done studies show little clear advantage for one recommendation over another.
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Adapted for this guideline from: American Academy of Pediatrics Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. Pediatrics 2004; 114(3):874–7.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

The final document was reviewed, using the Appraisal of Guidelines for Research and Evaluation (AGREE II) criteria by an external panel of metabolic dietitians, physicians and an expert in guideline development methodology who were not involved in the evidence analysis nor in the development phases of the maple syrup urine disease (MSUD) guideline.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is specifically stated for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Implementing the recommendations would:

- Reduce variations in clinical practice and services across medical centers
- Guide practice decisions that integrate medical and nutrition management/therapy
- Provide clinicians with criteria to make recommendations for nutrition management or recommend other treatments to achieve outcomes
- Design quality nutrition care based on a patient's metabolic and/or genetic alteration
- Improve patient outcomes and clinician effectiveness
- Enhance patient quality of life, prevent untoward consequences and complications and reduce associated medical, educational and social costs.

Potential Harms

Dietary restriction of the branched chain amino acids (BCAA) is complex and requires frequent monitoring and adjustment.

- Inappropriate intake of medical food can impact growth, nutritional status and overall health.
- Excessive intake of foods with intact protein can raise BCAA and α-ketoacids (BCKA) levels, cause metabolic decompensation, and have an impact on the central nervous system.
- Over-restriction of BCAA can impact growth and development and have very specific effects on various tissues of the body.
- During illness, catabolism increases the endogenous production of BCAA and puts the individual at risk for metabolic decompensation. Failure to adjust nutrient intake at this time, can be detrimental.
- Pregnancy in a woman with maple syrup urine disease (MSUD) involves not only the typical MSUD management, but also the increased needs of the pregnancy, the health of the fetus, the management of pregnancy-related illnesses and the rapid changes that occur after delivery.
- Liver transplantation may allow an individual with MSUD to consume a BCAA-unrestricted diet, but without nutritional counseling during the transition, nutrient needs may not be met.

Lack of appropriate nutrition management can result in negative consequences. This can be the result of implementing only some of the recommendations, failing to monitor outcomes, and failing to adjust nutrient intake in response to growth or illness.

Qualifying Statements

Qualifying Statements

Qualifying Statements

This nutrition management guideline is meant to serve as a framework for providing nutrition care to individuals with maple syrup urine disease (MSUD). It may not always be appropriate to use these guidelines. Individual circumstances and complicating conditions must be taken into consideration. The clinical judgment of the health care provider and patient preferences and values dictate treatment decisions. These nutrition management guidelines are provided with the express understanding that they do not establish or specify particular standards of care, whether legal, medical, or other.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Frazier DM, Allgeier C, Homer C, Marriage BJ, Ogata B, Rohr F, Splett PL, Stembridge A, Singh RH. Nutrition management guideline for maple syrup urine disease: an evidence- and consensus-based approach. Mol Genet Metab. 2014 Jul;112(3):210-7. [72 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 Jul

Guideline Developer(s)

Genetic Metabolic Dietitians International & Southeast Regional Newborn Screening and Genetics Consortium - Independent Expert Panel

Source(s) of Funding

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Guideline Committee

Maple Syrup Urine Disease (MSUD) Workgroup

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Financial Disclosures/Conflicts of Interest

Conflicts of Interest

- Dianne Frazier — received honoraria from Nutricia North America and Abbott Nutrition for consulting and lectures
- Courtney Allgeier — employee of Abbott Nutrition
- Caroline Homer — received honorarium for lecturing from Abbott Nutrition
- Barbara Marriage — employee of Abbott Nutrition
- Beth Ogata — none declared
- Frances Rohr — none declared
- Patricia Splett — none declared
- Adrya Stembridge — received funding from HRSA
- Rani Singh — received funding from HRSA

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the Molecular Genetics and Metabolism Web site .

Availability of Companion Documents

The HTML version of the guideline, with additional tables and other information, is available from the Southeast Regional Newborn Screening and Genetics Consortium Web site .

Patient Resources

Learning objectives for patients and family are available from the Southeast Regional Newborn Screening and Genetics Consortium Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on January 7, 2015. The information was verified by the guideline developer on March 13, 2015.

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